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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/576,628	04/04/2007	**Christian Peter Petzelt**	02839/46201	8178

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KENYON & KENYON LLP
ONE BROADWAY
NEW YORK, NY 10004

EXAMINER	
ARNOLD, ERNST V	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/576,628	PETZELT ET AL.	
	Examiner	Art Unit	
	ERNST V. ARNOLD	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 January 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-12 and 20-24 have been cancelled. Claims 13-19 are pending and under examination. Applicant's amendment has necessitated a new ground of rejection. The claims were examined on the basis of independent method claim 12 drawn to treating a human having an (a) aberrant or undesired apoptosis or (b) a disease associated with aberrant apoptosis. The basis of the 35 USC 112 first paragraph rejection was this limitation. However, claim 12 and limitations (a) and (b) have been cancelled and claims 13-15 are have been amended to independent claims drawn to three different methods no longer dependent on claim 12. This has necessitated a new ground of rejection. Accordingly, this Action is FINAL.

Withdrawn rejections:

Applicant's amendments and arguments filed 1/6/09 are acknowledged and have been fully considered. Any rejection and/or objection not specifically addressed below is herein withdrawn. Claims 12 and 16-24 were rejected under 35 U.S.C. 102(b) as being anticipated by WO 00/53192 (Hereinafter '192). Claims 12, 16 and 18-23 were rejected under 35 U.S.C. 102(b) as being anticipated by Franks et al. (US 6274633). Since these claims have been cancelled, the rejection is moot and is withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 14 recites the limitation "said human" in line 2. There is insufficient antecedent basis for this limitation in the claim.

Claim 15 recites the limitation "said human" in line 2. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 13-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for preventing or reducing cellular damage of tissue or organs to be transplanted in a human; preventing or reducing apoptotic cell death after eye laser surgery; protecting endothelial cells of the intestine in sepsis. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention without an undue amount of experimentation. This is a full enablement rejection.

Let the Examiner be clear: Applicant is not enabled for preventing or reducing cellular damage of tissue or organs to be transplanted in a human; preventing or reducing apoptotic cell death after eye laser surgery; protecting endothelial cells of the intestine in sepsis.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: 1) scope or breadth of the claims; 2) nature of the invention; 3) relative level of skill possessed by one of ordinary skill in the art; 4) state of, or the amount of knowledge in, the prior art; 5) level or degree of predictability, or a lack thereof, in the art; 6) amount of guidance or direction provided by the inventor; 7) presence or absence of working examples; and 8) quantity of experimentation required to make and use the claimed invention based upon the content of the supporting disclosure. When the above factors are weighed, it is the Examiner's position that one skilled in the art could not practice the invention without undue experimentation. While all of the factors have been considered, only those required for a prima facie case are set forth below.

2) Nature of the invention

The nature of the invention is directed to methods for treating a human comprising administering an effective amount of xenon for **preventing or reducing cellular damage of tissue or organs to be transplanted in a human; preventing or reducing apoptotic cell death after eye laser surgery; protecting endothelial cells of the intestine in sepsis.**

3) Relative level of skill possessed by one of ordinary skill in the art

From MPEP 2141.03: **The "hypothetical person having ordinary skill in the art' to which the claimed subject matter pertains would, of necessity have the capability of understanding the scientific and engineering principles applicable to the pertinent art**." *Ex parte Hiyamizu*, 10 USPQ2d 1393, 1394 (Bd. Pat. App. & Inter. 1988) (The Board disagreed with the examiner's definition of one of ordinary skill in the art (a doctorate level engineer or

scientist working at least 40 hours per week in semiconductor research or development), **finding that the hypothetical person is not definable by way of credentials**, and that the evidence in the application did not support the conclusion that such a person would require a doctorate or equivalent knowledge in science or engineering.). (Emphasis added).

4) State of, or the amount of knowledge in, the prior art

The art teaches that apoptosis is a complex series of cellular events (Taylor et al. Nature Reviews 2008, 9, 231-241; see figures 1-3 for example). The art teaches that xenon is a neuroprotectant because it is an NMDA antagonist ((page 1485 Abstract and introduction) Wilhelm et al. Anesthesiology 2002, 96, 1485-91).

Sepsis is a severe illness in which the bloodstream is overwhelmed by bacteria (MedlinePlus, medical encyclopedia: sepsis page 1 9/28/08).

Transplant rejection is when a transplant recipient's immune system attacks a transplanted organ or tissue (MedlinePlus, medical encyclopedia: Transplant rejection page 1; 2/15/07).

Graft versus host disease (GVHD) is a complication that can occur after a bone marrow transplant in which the newly transplanted material attacks the transplant recipient's body. Acute GVHD starts within the first 3 months after transplant and chronic GVHD starts more than 3 months after transplant and can last for 3 years or longer (MedlinePlus medical encyclopedia: graft versus host disease 7/11/08, page 1).

LASIK eye surgery is done with a laser that removes corneal tissue to reshape the lens (MedlinePlus Medical encyclopedia: LASIK eye surgery 8/17/07, page 1).

WO 00/53192 discloses the use of xenon or xenon gas mixtures for treating neurointoxications such as apoplexy (stroke), Parkinson's and craniocerebral trauma (Claims 1, 4, 7, 8 and 16). Franks et al. (US 6274633) claim a method of providing neuroprotection to a mammal in need thereof by administering an effective amount of xenon (claims 1 and 2). Xenon is thus well established in the art as a neuroprotectant.

5) Level or degree of predictability, or a lack thereof, in the art

Apoptosis is a complex mechanism where much is left unknown. Taylor et al. concede that "significant gaps remain in our knowledge of the process." (page 239 conclusions).

From Remington: The Science and Practice of Pharmacy 1995: "A drug may affect the response to another drug in a quantitative way. On the one hand, the intensity of either the therapeutic effect, or side effect, may be augmented or suppressed." (page 720, left column). And on page 723, lower left column, "*Multiple drug therapy should never be employed without a convincing indication that each drug is beneficial beyond the possible detriments or without proof that a therapeutically equivocal combination is definitely harmless*." (emphasis added). Therefore, drug combinations are highly unpredictable.

6) Amount of guidance or direction provided by the inventor

Applicant was required to provide in the specification additional guidance and direction with respect to how use the claimed subject matter in order for the application to be enabled with respect to the full scope of the claimed invention. Applicant performed a series of experiments on cortical neurons and HeLa cells by inducing apoptosis with staurosporine and treating with xenon. However, the art has already shown xenon to be a neuroprotectant and these results appear to be expected results. In addition, there is a lack of guidance in the specification as to

how one would extrapolate the cell based neuroprotection experiments to cellular damage, apoptotic cell death after laser eye surgery or protecting endotheilial cells against sepsis. Applicant has not provided any examples of **preventing or reducing cellular damage of tissue or organs to be transplanted in a human; preventing or reducing apoptotic cell death after eye laser surgery; protecting endothelial cells of the intestine in sepsis** that would guide or direct one of ordinary skill in the art to performing the instantly claimed methods.

7) Presence or absence of working examples

The specification fails to provide scientific data and working embodiments with respect to **preventing or reducing cellular damage of tissue or organs to be transplanted in a human; preventing or reducing apoptotic cell death after eye laser surgery; protecting endothelial cells of the intestine in sepsis.** In addition, the examples provided do not appear art recognized models for the claimed subject matter. How the experimental HeLa cells and neuronal cells correlate to the claimed cells of all tissue, organs, endothelial cells and ocular cells is unknown. The only experiments disclosed appear to confirm that which is already known in the art; that xenon protects cells (See examples 1 and 2 of WO 00/53192 and the disclosure of Petzelt et al. Life Sciences 2003, 72, 1909-1918).

8) Quantity of experimentation required to make and use the claimed invention based upon the content of the supporting disclosure

One of ordinary skill in the art would have to conduct a myriad number of experiments comprising determining dosage amounts of xenon/xenon gas mixtures; administration routes and then testing by trial and error every combination on patients, some of whom are suffering from severe bacterial infection (sespsis) and under transplant therapy. Clearly such patients will also

be treated with conventional therapeutic agents and as taught by Remingtons it is unpredictable how multiple drugs are going to interact. Without any guidance on how to extrapolate the data provided by Applicant or drug interactions with drugs used in the treatment of sepsis and transplant therapy, essentially one of ordinary skill in the art has to figure out how to do this themselves. As a result, one of ordinary skill in the art would be required to conduct an undue amount of experimentation to see if the method for preventing or reducing cellular damage of tissue or organs to be transplanted in a human; preventing or reducing apoptotic cell death after eye laser surgery; protecting endothelial cells of the intestine in sepsis actually works.

Genetech, 108 F.3d at 1366 states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable." (Genentech, Inc. v. Novo Nordisk, A/S, 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997)).

Response to arguments:

Applicant asserts that the data shows prevention. The Examiner cannot agree. Please note that the term "prevent" is an absolute definition which means to stop from occurring and, thus, requires a higher standard for enablement than does "therapeutic" or "treat". Clearly in Figure 4, not all the caspase activity was prevented. Also in Figure 1 and 2, some LDH release is present. In no example is 100% activity inhibition achieved or 100% LDH release inhibited. Therefore, Applicant is not enabled for prevention which is an absolute definition. It must work 100% of the time for enablement.

Applicant asserts that the data shown with HeLa and cortical neuronal cells demonstrates the dramatic effects in widely disparate cell types. Applicant's argument is predicated on the premise that all cells have caspases for apoptotic cell death but this has not been demonstrated. While the Examiner understands the mechanism by which xenon is exerting the beneficial effect, there is a gargantuan leap of logic to go from the data presented and the claimed subject matter. The information contained in the disclosure of an application must be sufficient to inform those skilled in the relevant art how to both make and use the claimed invention. Claim 13 broadly encompasses all tissue and organs to be transplanted and nothing has been shown that all cells/tissues/organs can have prevented/reduced cellular damage through caspase 3/7. Cellular damage can be caused by autoimmune responses as discussed above. How is the instant invention going to prevent that? In LASIK, tissue is removed so what does it matter if the removed tissues suffers apoptotic cell death? The removed tissue is expected to die after removal. How is the instant invention going to prevent that? Sepsis is a severe illness with bacteria overwhelming the bloodstream which is a serious medical condition and one of ordinary skill in the art is supposed to believe that because xenon has some beneficial effect on staurosporine treated Hela and cortical neuronal cells that, magically, endothelial cells can be protected in sepsis? In claims 14 and 15, the cells/tissue of the eye as well as the endothelial cells of the intestine are not HeLa cells or cortical neuronal cells. Applicant has merely made broad sweeping claims without any proof. No examples of cells from the eye or intestine or other tissue or organs were tested. Applicant asserts on page 11 of the Remarks: "The death of cells that occurs when tissues or organs are transplanted, after eye laser surgery, or during sepsis is largely

brought about by apoptosis." This is an assertion without reference. "Largely" does not mean entirely and therefore some death of cells occurs by other means.

In conclusion, Applicant has shown reduced caspase activity in HeLa and cortical neuronal cells challenged by staurosporine and treated with xenon. On the one hand, this appears to be an expected result because xenon is known to be a neuroprotectant as taught by WO 00/53192 and Franks et al. (US 6274633). On the other hand, based on this data, it appears Applicant desires a leap of faith that administration of xenon performs the methods as claimed. Furthermore, there is nothing in the art which would suggest that this finding can be extrapolated to preventing or reducing cellular damage of in tissue or organs to be transplanted in a human; preventing or reducing apoptotic cell death after eye laser surgery; or protecting endothelial cells of the intestine in sepsis. The critical bridging information needed to go from the experimental data to the claimed subject matter is missing and without that information one of ordinary skill in the art simply cannot perform the method as claimed and it would require an unreasonable amount of experimentation to try and figure out how to make this invention work. Thus, the teachings set forth in the specification provide no more than a "plan" or "invitation" for those of skill in the art to experiment. Applicant's arguments are not persuasive and the rejection is maintained.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ERNST V. ARNOLD whose telephone number is (571)272-8509. The examiner can normally be reached on M-F 6:15-3:45.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Ernst V Arnold/
Examiner, Art Unit 1616